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FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,071	BRONNER ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *5-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *10/01/04*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of groups 1-4, claims 1-4, SEQ ID No: 2, 4, 6 and 8, and further election of SEQ ID NO:2, in Paper pf 09/24/04 is acknowledged and entered.

In a telephonic interview with Stephen Maebius on 11/01/04, Applicant asserts that Applicant meant election of only group 1, claims 1-4, SEQ ID NO:2, and that the recitation of election of groups 1-4 is a typographic error.

Claims 1-39 are pending in the instant application and Claims 5-39 have been withdrawn from further consideration by the Examiner under 37 CFR 1.142(b) as being drawn to non-elected invention.

Group 1, Claims 1-4, SEQ ID NO:2, are currently under prosecution.

The traversal is on the following ground(s):

Applicant argues that this Application is a 371 application, and yet the Examiner applies the US practice.

Applicant further argues that group 5, claims 5-8, 12, 24, 26, drawn to the DNA of SEQ ID NO:1, which encodes SEQ ID NO:2 should be rejoined with group 1, because unity of invention does exist between claims 1-4 and claims 5-8, 12, 24, 26.

Applicant argues that group 9, claims 9-10, 23, 25 and group 13, claim 11, drawn to various use of the polynucleotide of SEQ ID NO:1, and thus should be rejoined with groups 1, 5.

The Examiner apologizes for inadvertently applying the US standard for the reasons for lack of unity for the instant application.

The following is the reasons for restriction requirement for groups 1-16, as required under 35 U.S.C. 121 and 372.

This application contains 1-16 inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.2.

A national stage application is considered to have unity of invention where there exists a "special technical feature" that defines a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. See PCT Rule 13.2,' 37 CFR 1.475(a), (b)(1) and (2).

According to PCT Rule 13.2, unity of invention exists only when the shared same or corresponding technical feature is a contribution over the prior art. The inventions listed as groups 1-16 do not relate to a single general inventive concept because their same or corresponding technical feature is not a contribution over the prior art. The polypeptide comprising a fragment of at least 5 consecutive amino acids of SEQ ID NO:2 of group 1 is known in the art, as shown by US 6,583,275, which teaches SEQ ID NO:4608, which is 100% similar to SEQ ID NO:2, from amino acid 599 to amino acid 606, as shown by MPSRCH sequence similarity search report, 2004, us-10-019-071-2.olig.rai, pages 1-2. Thus considered as a whole, the shared technical feature of the inventions of group 1 lacks novelty or inventive step, and does not make a contribution over the prior art. Accordingly, the instant application lacks unity of invention.

Accordingly, Group 1, Claims 1-4, SEQ ID NO:2, are currently under prosecution.

PRIORITY DATE

The Examiner has established a priority date (06/22/200) for the instantly claimed application serial number 10/019071 as a certified, English translated copy the application FRANCE 99/07935 filed on 06/22/1999, to which priority is claimed, is not available.

SEQUENCE RULE

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821-25 for the following reasons:

The specification recites sequences that are not accompanied by a sequence identification number, for example, figures 6, 7, 9 legends on pages 37-38, and the sequences ICBP90 (89,758 kDa, p.37, lines 23-24) and ICBP-59 (59 kDa, p.43, lines 23-24).

INFORMATION DISCLOSURE STATEMENT

The information disclosure statement and PTO-1449 are missing in the application, although some prior art references have been received.

OBJECTION

1. Claim 3 is objected to for the use of the language "fixation". It is not clear what type of fixation is referred to. This rejection could be ovecome, by amendment of the claim, for example, to replace "fixation" with a more commonly used term "binding".

2. Claim 4 is objected to for the use of the language "preferably" which is a relative term.

3. The specification is objected to, concerning the layout of the specification. For example, the subtitles BRIEF SUMMARY OF THE INVENTION, BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S) and DETAILED DESCRIPTION OF THE INVENTION are missing.

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.

(b) CROSS-REFERENCE TO RELATED APPLICATIONS.

(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.

(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or

REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)

(e) BACKGROUND OF THE INVENTION.

(1) Field of the Invention.

(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(f) BRIEF SUMMARY OF THE INVENTION.

(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).

(h) DETAILED DESCRIPTION OF THE INVENTION.

(i) CLAIM OR CLAIMS (commencing on a separate sheet).

(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).

(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claims 2-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 2-4 are indefinite for the use of the language "biologically active fragment" in claim 2. It is not clear what type of biological activity is referred to.

The specification discloses that "it shall be understood that the term "biologically active fragment" designates in particular a fragment of an amino acid sequence of a polypeptide according to the invention having "at least" one of the functional characteristics or properties of the polypeptides according to the invention, notably in that: (i) it is capable of being recognized by a specific antibody of a polypeptide according to the invention; (ii) it has at least one of the domains or regions as defined above; (iii) it is capable of binding to DNA and notably to the CCAATT and/or inverted CCAAT boxes; (iv) it is capable of modulating the expression rate of the gene of topoisomerase II alpha, (v) it is capable of modulating cell proliferation (p.10, second paragraph).

The definition of "biologically active fragment", however, is not limiting. Thus one would not know what type of biological activity is referred to, and one cannot determine the metes and bound of the claimed invention.

2. Claims 3-4 are indefinite, because Claim 3 recites the limitation "the DNA" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

REJECTION UNDER 35 USC 101, UTILITY

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1-4 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific, substantial asserted utility or a well established utility.

Claims 1-4 are drawn to the ICBP90 protein of SEQ ID NO:2, that binds to the CCAAT box, preferably an inverted CCAAT box, a variant thereof, a homologous polypeptide having at least 80%, preferably 90% homology with SEQ ID NO:2, a polypeptide comprising 1) a fragment of at least 5 consecutive amino acids of SEQ ID NO:2 or a variant thereof, 2) a biologically active fragment of SEQ ID NO:2 or a variant thereof or 3) at least one domain for fixation to the DNA composed of a zinc-finger domain or a leucine-zipper domain.

The specification discloses isolation of the polypeptide of SEQ ID NO:2, ICBP90, having a molecular weight of 97kDa in acrylamide gel, and its C-terminal fragment ICBP59, having a molecular weight of 59 kDa, which bind to the oligonucleotides containing three tandem copies of inverted CCAAT boxes ICB1 or ICB2 (Example 1, pages 40-51, especially page 42, lines 19-33, bridging page 43, page 46, second paragraph, and page 49, second paragraph).

The specification speculates that the ICBP90 of SEQ ID NO:2 could play an important role in cellular proliferation, by binding to the CCAAT boxes of genes such as topoisomerase IIa, which in general has higher activity in cancer cells as compared to normal cells, and modulates the expression of the genes (p.49, third paragraph, p.51, second paragraph).

The specification discloses that in both confluent and proliferating Hela cells, a 97 kDa band is detected by the monoclonal antibody to ICBP59, however the proliferating Hela cells also have a band at 85 kDa which is not found in confluent Hela cells (figure 1 legend on pages 34-35). The specification discloses that however only proliferating normal fibroblast cell line expresses the 97kDa band as compared to the confluent fibroblast cell line (figure 1 legend). The specification discloses that the leukemia cell line MOLT-4 also expresses the 97 kDa protein (figure 11B).

The specification discloses the mRNA encoding the ICBP90 protein is detected in human tissues, most abundantly in thymus and adult bone marrow and fetal liver (figure 5 legend on pages 36-37).

The specification discloses in figure 8, and on page 37 that an elevated level of IICBP90 protein is detected in sera of patients with solid tumors.

The specification speculates that the claimed polypeptide could be used to assess the proliferative state of a given cancerous tissue for diagnostic purpose (p.50, second paragraph).

The specification speculates that antibodies to the claimed polypeptide could be conjugated to cytotoxic agent for treating cancer (p.32-33).

The specification discloses that by double hybrid technique, ICBP90 interacts with TIP60, a coactivator protein of the nuclear receptor, especially receptor for androgens, and thus ICBP90 may play a role in nuclear receptor (p.65, first paragraph).

It is noted that in figure 8, there is no control sample of normal sera, and thus one cannot determine whether there is overexpression of SEQ ID NO:2 in sera of cancer patients as compared to normal control sera.

Neither the specification nor any art of record teaches what SEQ ID NO:2 is; they do not teach a utility for SEQ ID NO:2 or any of the fragments claimed; they do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases.

The asserted utilities for SEQ ID NO:2, such as production of and screening of antibodies per se apply to many unrelated polypeptide structures sequences. Therefore the asserted utilities are not considered "specific" utilities, i.e. they are not specific to SEQ ID NO:2.

Additional disclosed utilities for SEQ ID NO:2 include therapy and diagnosis of conditions and diseases such as cancers. However, there is no association between SEQ ID NO:2 and cancer or any disease. Additional work must be done to determine if SEQ ID NO:2 is associated with cancer or any diseases.

The asserted diagnostic and therapeutic utility of SEQ ID NO:2 is based on the assumption that 1) via binding to an oligonucleotide containing the consensus sequence CCAAT boxes found in some promoters, the polypeptide of SEQ ID NO:2 would bind to the promoter of genes such as topoisomerase II, and regulate gene expression such as

cell proliferation, 2) SEQ ID NO:2 is found in two cancer cell lines and in a proliferative normal fibroblast, but not in confluent normal fibroblast cell line, 3) an elevated level of IICBP90 protein is detected in sera of patients with solid tumors, and 4) SEQ ID NO:2 interacts with TIP60, a coactivator protein of the nuclear receptor, especially receptor for androgens.

A. However, there is no evidence that SEQ ID NO:2 binds to any gene, including topoisomerase IIa via the CCAAT boxes in its promoter and regulates its gene expression. Although SEQ ID NO:2 binds to an oligonucleotide sequence containing the CCAAT boxes, one cannot determine that SEQ ID NO:2 actually binds to any full length gene via the CCAAT boxes, especially in vivo, and regulate gene expression, because it is well known in the art that a specific binding of a ligand to a substrate requires specific interaction between the ligand and the substrate, and correct conformation of the ligand to fit into the binding site of the substrate, e.g. specific binding between a ligand and a receptor, or between an antigen and an antibody. One cannot predict that SEQ ID NO:2 would have the necessary conformation for binding to the CCAAT boxes, which are of unknown conformation when they are within the three dimensional configuration of full length genes. The following teaching of Bowie et al (Science, 1990, 247: 1306-1310, especially columns 1-2, p.1306), although drawn to proteins, would apply as well to polynucleotides which encode protein. Bowie et al teach that the ability of proteins to fold into unique three-dimensional structures depends on the amino acid composition of the protein. In addition, Ronchi, A et al, 1995, Nucleic acids Res, 23(22): 4565-72, teach that the CCAAT-box binding protein NF-Y recognizes and binds to a minor groove

in the target DNA and distorts or bends the target DNA, and that the nucleotides flanking the CCAAT pentanucleotide influence the degree of bending. Liberati, C et al, 1999, J Mol Biol, 285(4) : 1441-55 teach that precise alignment of two CCAAT boxes, 32 bp, three turns of the helix, is essential for recognition by and co-operative interactions among the units of the trimer CCAAT-binding protein, NF-Y (CBF). Further, Sugiura et al, 2003, FEBS letters, 537(1-3): 58-62 teach that interaction between a CCAAT-binding protein, such as NF-Y, and a 3'-flanking region of 15 bp downstream of the CCAAT box results in conformational change of the protein, and significantly alters the affinity of the binding, and thus the stability of the binding of said CCAAT-binding protein to its specific target DNA sequence.

The specification however does not disclose whether SEQ ID NO:2 could interact with DNA sequence 3'-flanking the CCAAT box of topoisomerase IIa, such as a 15 bp downstream of the CCAAT box taught by Sugiura et al, such that the binding to SEQ ID NO:2 to topoisomerase IIa would be of high affinity and stable.

Since the conformation of the polynucleotide sequence surrounding the CCAAT boxes, to which the claimed polypeptide is supposed to bind, could not be predicted, and in view of the above teaching in the art that precise recognition of and binding to the region surrounding the CCAAT box(es) is required, and that sequences flanking the CCAAT boxes could significantly alter the affinity and stability of the binding of CCAAT binding protein to the target DNA, one cannot predict that the binding region of SEQ ID NO:2 would fit into the three-dimensional structure surrounding the CCAAT boxes of full length genes such as topoisomerase IIa, nor one can predict in vivo adequate and

stable binding of the claimed polypeptide to the consensus sequence CCAAT boxes of the promoter of topoisomerase IIa, which is necessary for its successful regulation of expression of said gene, or regulation of cell proliferation.

Further experimentation is required to determine whether SEQ ID NO:2 binds to and regulates expression of genes such as topoisomerase IIa, which is related to cell proliferation.

Further, there is no teaching of how to target the claimed polypeptide through both extracellular and nuclear membranes to reach the target gene. A therapeutic agent must accomplish several tasks to be effective. It must be delivered into the circulation that supplies the target cells and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. In addition the target cell must not have a alternate means of survival despite action at the proper site for the drug. In addtion variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The polypeptide may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life of the protein and the *in vitro* tests of record do not sufficiently duplicate the conditions which occur *in vivo*. In addition, the polypeptide may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the polypeptide has no effect, circulation into the target area may be insufficient to carry the polypeptide and a large enough local concentration may not be established.

Further experimentation is required to determine whether SEQ ID NO:2 could be useful in regulation of expression of genes such as topoisomerase IIa, or regulation of cell proliferation.

B. Further, although SEQ ID NO:2 is found in two cancer cell lines and in a proliferative normal fibroblast, but not in confluent normal fibroblast cell line, one cannot determine that SEQ ID NO:2 could be used for diagnosis of cancer, because there is no correlation between expression of cells in cultures and that of primary cancer tissues, due to cell culture artifacts. Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal

constitutions (see abstract). Thus based on the teaching in the art, one cannot predict that cancer tissue expresses SEQ ID NO:2, and not in corresponding normal, non-proliferating tissue.

Moreover, in figure 8, there is no control sample of normal sera, and thus one cannot determine whether there is overexpression of SEQ ID NO:2 in sera of cancer patients as compared to normal control sera

Further experimentation is required to determine whether SEQ ID NO:2 could be useful for detecting cancers as claimed in the specification.

C. Further, one cannot determine that SEQ ID NO:2, or antibodies for SEQ ID NO:2 could be used for treating cancer, as contemplated, since there is no correlation between SEQ ID NO:2 and cancer, supra, and since cancer treatment is unpredictable. for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of objective evidence, no one skilled in the art would accept the assertion that the claimed polypeptide could be used for treating cancers. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in

the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2). Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to

prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler (Cancer Biotherapy, 1995, 10:1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1). Furthermore, Boon (Adv Can Res, 1992, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2).

Thus, based on the teaching in the art, one cannot predict that SEQ ID NO:2 or its antibodies could be useful for treating cancers.

Further experimentation is required to determine whether SEQ ID NO:2 could be useful in treating cancer.

D. Moreover, although SEQ ID NO:2 binds to TIP60 protein, a coactivator protein of the nuclear receptor, especially receptor for androgens, one cannot determine which use could be inferred from binding to the TIP60 protein, because binding to a protein per se, such as binding of an antibody to a protein, would not necessarily lead to regulation of said protein. There is no indication that binding to the TIP60 protein would

result in any regulation of any nuclear receptor that can be of any practical use. Further experimentation is required to determine what use is for the claimed polypeptide.

In the absence of any disclosed relationship between the claimed polypeptide and any disease or disorder and the lack of any correlation between the claimed polypeptide with any known disease or disorder, and further in view that any potential diagnostic or therapeutic utility is not yet known and has not yet been disclosed, the utility is not substantial. Further research is necessary to determine what use is for the claimed polypeptide. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPO at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. 101.

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptide. Because the claimed invention is not supported by a specific, substantial asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph.

A. Specifically, since the claimed invention is not supported by specific, substantial utility or a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

B. If Applicant could overcome the above 101 and 112, first paragraph rejection, claims 2-4 are still rejected under 112, first paragraph, for lack of enablement for "a variant" of SEQ ID NO:2, a polypeptide having at least "80%, preferably 90% homology" with SEQ ID NO:2, a polypeptide "comprising" : 1) a fragment of at least 5 consecutive amino acids of SEQ ID NO:2 or a variant thereof, 2) a biologically active fragment of SEQ ID NO:2 or a variant thereof or 3) at least one domain for fixation to the DNA composed of a zinc-finger domain or a leucine-zipper domain.

It is noted that a variant polypeptide of SEQ ID NO:2, or a polypeptide having at least "80%, preferably 90% homology" with SEQ ID NO:2 encompasses variants of SEQ ID NO:2, wherein said variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the peptide, as well as insertions and deletions.

It is further noted that a polypeptide "comprising" : 1) a fragment of at least 5 consecutive amino acids of SEQ ID NO:2 or a variant thereof, 2) a biologically active fragment of SEQ ID NO:2 or a variant thereof or 3) at least one domain for fixation to the DNA composed of a zinc-finger domain or a leucine-zipper domain encompasses sequences with unknown structure and function that are attached to a fragment which could be as little as 5 amino acids of SEQ ID NO:2, or attached to a zinc-finger domain or a leucine-zipper domain.

Moreover, it is noted that there is no teaching of the structure of the claimed biological active fragment, in view that the definition of "biological active fragment" is not limiting, supra, and it is not clear what type of biological activity is referred to.

Applicant has not shown how to make and use the claimed polypeptide variants which are capable of functioning as that which is being disclosed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, p.1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitution can be made with a

reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, p.1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al, (Journal of Cell Biology, 1990, 11: 2129-2138), who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

In addition, although some conservative subsititution would not necessarily destroy the biological function of a protein, the specification fails to disclose which amino acid(s) are naturally subjected to conservative substitution. In the absence of a source of method of making such variants, one of skill in the art would be forced into undue experimentation to practice the claimed invention as broadly as claimed.

Further, there is no teaching which structure of the numerous sequences, that are attached to the zinc-finger or the leucine-zipper domain, such that the claimed sequences would have the function and characteristics of SEQ ID NO:2, because the

zinc-finger or the leucine-zipper domain would only at most confer binding to a DNA sequence, and because binding to a DNA sequence per se would not be sufficient to confer the function and characteristics of SEQ ID NO:2.

In view of the above unpredictability, one of skill in the art would be forced into undue experimentation in order to use the claimed invention as broadly as claimed.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 2-4 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 2-4 are drawn to "a variant" of SEQ ID NO:2, a polypeptide having at least "80%, preferably 90% homology" with SEQ ID NO:2, a polypeptide "comprising" : 1) a fragment of at least 5 consecutive amino acids of SEQ ID NO:2 or a variant thereof, 2) a biologically active fragment of SEQ ID NO:2 or a variant thereof or 3) at least one domain for fixation to the DNA composed of a zinc-finger domain or a leucine-zipper domain.

It is noted that a variant polypeptide of SEQ ID NO:2, or a polypeptide having at least "80%, preferably 90% homology" with SEQ ID NO:2 encompasses variants of SEQ ID NO:2, wherein said variants have any type of substitution besides conservative

substitution, at any amino acid, throughout the length of the peptide, as well as insertions and deletions.

It is further noted that a polypeptide "comprising" : 1) a fragment of at least 5 consecutive amino acids of SEQ ID NO:2 or a variant thereof, 2) a biologically active fragment of SEQ ID NO:2 or a variant thereof or 3) at least one domain for fixation to the DNA composed of a zinc-finger domain or a leucine-zipper domain encompasses sequences with unknown structure and function that are attached to a fragment which could be as little as 5 amino acids of SEQ ID NO:2, or attached to a zinc-finger domain or a leucine-zipper domain.

Moreover, it is noted that there is no teaching of the structure of the claimed biological active fragment, in view that the definition of "biological active fragment" is not limiting, supra, and it is not clear what type of biological activity is referred to.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, "requires a precise definition, such as by structure, formula, [or] chemical name," of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted

the standard that the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here.

Thus, the instant specification may provide an adequate written description of a variant of SEQ ID NO:2, or a polypeptide comprising a fragment of SEQ ID NO:2, or a polypeptide minimally comprising a zinc-finger domain or a leucine-zipper domain, per Lilly by structurally describing a representative number of variants of SEQ ID NO:2, or polypeptides comprising a fragment of SEQ ID NO:2, or polypeptides minimally comprising a zinc-finger domain or a leucine-zipper domain or by describing structural features common to the members of the genus, which features constitute a substantial portion of the genus. Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe a variant of SEQ ID NO:2, or a polypeptide comprising a fragment of SEQ ID NO:2, or a polypeptide minimally

comprising a zinc-finger domain or a leucine-zipper domain required to practice the claimed invention in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any variant of SEQ ID NO:2, or any polypeptide comprising a fragment of SEQ ID NO:2, or any polypeptide minimally comprising a zinc-finger domain or a leucine-zipper domain, other than SEQ ID NO:2, nor does the specification provide any physical or chemical characteristics of variant of SEQ ID NO:2, or a polypeptide comprising a fragment of SEQ ID NO:2, or a polypeptide minimally comprising a zinc-finger domain or a leucine-zipper domain, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single polypeptide of SEQ ID NO:2, this does not provide a description of a variant of SEQ ID NO:2, or a polypeptide comprising a fragment of SEQ ID NO:2, or a polypeptide minimally comprising a zinc-finger domain or a leucine-zipper domain, that would satisfy the standard set out in Enzo.

The specification also fails to describe variant of SEQ ID NO:2, or a polypeptide comprising a fragment of SEQ ID NO:2, or a polypeptide minimally comprising a zinc-finger domain or a leucine-zipper domain by the test set out in Lilly. The specification describes only a single polypeptide of SEQ ID NO:2. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of a variant of SEQ ID NO:2, or a polypeptide comprising a fragment of SEQ ID NO:2, or a polypeptide minimally comprising a zinc-finger domain or a leucine-zipper domain, that is required to practice the claimed invention.

REJECTION UNDER 35 USC 102(e)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

1. Claims 1-4 are rejected under 35 U.S.C. 102(e) as being anticipated by Hopfner, R et al, Jan 01, 2000, Cancer Res, 60(1): 121-128.

Claims 1-4 are drawn to an isolated ICBP90 protein of SEQ ID NO:2, that binds to the CCAAT box, preferably an inverted CCAAT box, a polypeptide comprising 1) a fragment of at least 5 consecutive amino acids of SEQ ID NO:2, or 2) a biologically active fragment of SEQ ID NO:2, or a polypeptide comprising at least one domain for fixation to the DNA composed of a zinc-finger domain or a leucine-zipper domain, wherein the DNA is a CCAAT box, preferably an inverted CCAAT box.

Hopfner, R et al teach ICBP90 protein, a CCAAT binding protein, which has a zinc finger domain and a ring finger domain, a putative leucine zipper domain (figure 2 on page 124). The sequence taught by Hopfner et al is 100% similar to the full length of SEQ ID NO:2, from amino acid 1 to amino acid 793, as shown by MPSRCH sequence similarity search (MPSRCH search report, 2004, us-10-019-071-2.rup, pages 1-2).

2. Claim 2 is rejected under 35 U.S.C. 102(e) as being anticipated by US 6,551,795 or US 6,583,275.

Claim 2 is drawn to a polypeptide comprising a fragment of at least 5 consecutive amino acids of SEQ ID NO:2.

US 6,551,795 teaches SEQ ID NO:20583, which is 100% similar to SEQ ID NO:2, from amino acid 615 to amino acid 623, as shown by MPSRCH sequence similarity search (MPSRCH search report, 2004, us-10-019-071-2.olig.rai, page 1).

US 6,583,275 teaches SEQ ID NO:4608, which is 100% similar to SEQ ID NO:2, from amino acid 599 to amino acid 606, as shown by MPSRCH sequence similarity search (MPSRCH search report, 2004, us-10-019-071-2.olig.rai, pages 1-2).

The sequence taught by US 6,551,795 or US 6,583,275 clearly meets all the limitation of the claim, i.e. comprising a fragment of at least 5 consecutive amino acids of SEQ ID NO:2.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS